

REMARKS

In this Amendment, claim 1 has been amended; claims 2-37, 60-75 and 77-89 were previously presented; and claims 38-59 and 76 are cancelled without prejudice or disclaimer. New claims 90-96 have been added to more completely describe Applicants' invention and to place the application in form for allowance or in better condition for appeal. The amended and new claims are fully supported by the instant specification. Accordingly, no new matter is introduced by the amended and new claims.

More specifically, support for coating the dried solid microparticles with a release rate-controlling shell of a biocompatible and biodegradable polymer as described in presently amended claim 1 is found in the instant specification, *inter alia*, on page 37, lines 16-19 and lines 34 and 35. Support for the release-controlling shell comprising PLGA and the application of the shell by air suspension technology as described in new claims 90-96 is found in the instant specification, *inter alia*, on page 37, lines 16-23. Support for the use of an organic solvent in step (h) of the new claims 92, 95 and 96 is found in the instant specification, *inter alia*, on page 49, Example 3.

It is submitted that the new claims, which have been added to more completely describe aspects of Applicants' invention and to place the claims in form for allowance or in better form for appeal, closely track the previously presented claims and introduce no new matter into the application. Accordingly, the presently pending claims in this application are claims 1, 2-37, 60-75 and 77-96.

Double Patenting

Claims 1-37, 60-75 and 77-89 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-19 of U.S. Patent No. 6,616,949 ('949) and over claims 1-19 of U.S. Patent No. 6,706,288 ('288). According to the Examiner, the conflicting claims are not identical, but are considered not patentably distinct from each other.

Applicants submit herewith a terminal disclaimer and the required fee therefor in response to this rejection. Accordingly, withdrawal of the rejection is respectfully requested.

The claims fulfill the requirements of 35 U.S.C. § 103(a)

Claims 1-37, 60-75 and 77-89 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Woiszwilllo *et al.* (U.S. Patent No. 5,981,719), hereinafter "Woiszwilllo", and Ekman *et al.* (U.S. Patent No. 4,822,535), hereinafter "Ekman", in view of Laakso *et al.* (*J. Pharm. Sci.*, 1986, 75(10):962-967, hereinafter "Laakso", and Takada *et al.* (U.S. Patent No. 5,622,657), hereinafter "Takada".

The rejection of the claims under 35 USC § 103(a) is respectfully traversed. Applicants respectfully contend that the Examiner has not established a *prima facie* case of obviousness under 35 U.S.C. § 103 as a basis for rejection of these claims.

It is respectfully submitted that the presently claimed invention must be considered as a whole in determining differences between the prior art and the presently claimed invention. M.P.E.P. §2141.02. Considered in its entirety, the presently claimed invention is directed to a process involving the formation of a concentrated biologically active substance, e.g., a concentrated solution or a solid particle precipitate of the biologically active substance, when mixed with polyethylene glycol. The concentrated biologically active substance is mixed with starch solution prior to drying and solidification into microparticles. See, e.g., page 20, lines 8-11 of the instant application, (paragraphs [0046]-[0052] of the published application no. US 2002/0081336 A1). In Applicants' process, the biologically active substance is in a concentrated form; therefore, the biologically active substance is stabilized in the microparticles and does not distribute out into the outer phase during microparticle preparation. (See, page 21, lines 4-6 of the instant application, (paragraph [0055] of the published application no. US 2002/0081336 A1).

Applicants' presently claimed process can additionally involve a step in which the outer surface of the dried, solid starch particles is coated with a release rate-controlling exterior shell or coating. This outer shell or coating is applied to the dried starch microparticles containing a biologically active substance after solid microparticles are formed, for example, by an air

suspension technique. As taught by Applicants, the coating step involves the use of organic solvents. (See, e.g., Example 3, page 49 of the instant specification as filed). Such organic solvents do not adversely affect the biologically active substances contained in Applicants' microparticles. This is because these substances are concentrated and immobilized in the starch microparticles, which are dried and solidified in accordance with Applicants' process before the polymer coating is applied to the formed, solid microparticles. Thus, in the practice of Applicants' presently claimed invention, the organic solvents employed in the coating step do not degrade the solvent-sensitive biologically active substances. It is submitted that the cited art, alone or combined, does not teach or suggest Applicants' process of preparing solid starch microparticles and then coating the dried solid microparticles with a release controlling polymer, which is performed in the presence of an organic solvent.

It is further submitted that all claim limitations must be taught or suggested by the cited art reference. M.P.E.P. §2143.03. However, in this instance, the applied references, alone or in combination, do not teach or suggest all of the limitations of Applicants' presently claimed invention. For example, neither Woiszwilllo nor Ekman, alone or combined, in view of Laakso and Takada, teaches a process in which a concentrated form of a biologically active substance is formed from an emulsion into starch microparticles that are dried into solid form and then are coated, if desired, with a release rate-controlling polymer, such as, for example, PLGA, in the presence of an organic solvent.

As discussed at length in Applicants' previously-submitted response, Woiszwilllo discloses and teaches a method that is distinct from Applicants' presently claimed invention. Woiszwilllo's method comprises an aqueous-based system that does not involve any water-in-oil emulsion. Indeed, it is a stated object in Woiszwilllo's disclosure that a water-in-oil emulsion is not used in the manufacture of Woiszwilllo's microparticles. This stands in direct contrast with Applicants' presently claimed process in which an emulsion containing starch droplets is employed. More specifically, Woiszwilllo plainly discloses that:

[i]t is a further object of the present invention to provide a process for making microparticles that uses only aqueous or aqueous miscible solvents and does not utilize a water-in-oil emulsion in

the manufacturing of the microparticles. (Col. 4, lines 21-24,
Emphasis added).

Woiszwilllo's above-cited disclosure also clearly imparts to the skilled practitioner in this art that Woiszwilllo's method would not be part of, or combined with, a method utilizing emulsions involving water and oil, such as that of Ekman. Because Woiszwilllo teaches as its contemplated invention a process for making microparticles, which is carried out using water or water miscible solvents in the absence of an emulsion (Col. 4, lines 17-19 of Woiszwilllo), a combination of Woiszwilllo's method with Ekman's method does not contain all of the elements of Applicants' presently claimed invention and does not make obvious Applicants' presently claimed process.

Turning to Ekman, Applicants submit that on page 6 of the 12/28/04 Office Action, the Examiner characterizes Ekman as teaching a method "to encapsulate bioactive substance in order to form solid microparticles by employing a two-phase emulsion system." (Emphasis added). This teaching is disclosed by Ekman at Col. 8, lines 18-35. It is pointed out that Ekman's teaching and method are clearly distinguished from Applicants' presently claimed process, as well as from the method taught and disclosed by Woiszwilllo.

For example, a plain reading of Ekman's disclosure shows that Ekman teaches and describes a method of producing microparticles in which a macromolecular, e.g., bioactive, substance is "enclosed or entrapped", i.e., "encapsulated", in the particles as they are formed. (See, Col. 8, lines 8-17 of Ekman). Specifically, Ekman states:

In accordance with a further aspect of the invention, one or more substances, which are inert during the process of converting the droplets to a solid form and which preferably are macromolecular substances, may be included as dissolved substances in the dispersed phase and be enclosed or entrapped in the particles as they form. (Col. 8, lines 8-14; Emphasis added).

In addition, also whole (living) cells, cell organelles, solid particles or small oil droplets can be encapsulated when practicing this invention. (Col. 8, lines 15-17 of Ekman).

Thus, it is clear that Ekman only teaches entrapping, enclosing, or encapsulating substances, i.e., macromolecular substances, within the particles as they are being formed during the practice of Ekman's method. Ekman does not teach coating pre-formed, solid microparticles with polymer. It is also understood from Ekman's teaching and disclosure that the terms "enclosing", "entrapping" and "encapsulating" are used as synonymous terms to describe that a substance is enveloped within or contained inside of microparticles when the microparticles are being formed using the methods as taught by Ekman's various embodiments. (See, e.g., Col. 8, lines 18-40 of Ekman). Ekman's teaching and methods are in sharp contrast to Applicants' claimed process in which a bioactive substance in concentrated form is mixed with starch solution, following which, the mixture in the presence of an aqueous solution forms a two-phase system comprising an emulsion of starch droplets that contain the bioactive substance as the inner phase in an outer phase of polymer solution. Thereafter, according to Applicants' process, the starch droplets containing the bioactive substance are dried and solidified, and after this, the so-formed solid microparticles may be externally coated with a release-controlling polymer.

Moreover, as noted in MPEP §2143.01, with reference to *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990):

The mere fact that references can be combined or modified does not render the resultant combination obvious unless **the prior art suggests** the desirability of the combination. (Emphasis added).

Applicants respectfully contend that the Examiner has not provided evidence, either in the cited references or in the art as a whole, of a valid suggestion or motivation to combine and/or modify the disclosures of Woiszwilllo and Ekman, in view of Laakso and Takada, to produce the process of the present invention. There is also no evidence other than conclusory statements provided by the Examiner to suggest that the combined disclosures of Woiszwilllo and Ekman would lead to the achievement of the presently claimed invention.

In fact, the Examiner states on the one hand that the cited references "do not expressly teach [Applicants'] method of preparing microparticles by employing the method of Woiszwilllo followed by that of Ekman" (12/28/04 Office Action, page 7), and on the other hand makes a conclusory statement, without actual support or evidence, that "it would have been obvious to

one of ordinary skill in the art at the time the invention was made to prepare [Applicants'] claimed microparticles by employing the method of Woiszwillo followed by that of Ekman." The Examiner concludes that "Woiszwillo's method is to prepare a microparticle and then Ekman *et al.* would further encapsulate such microparticle to increasing [*sic*] the stability of the biological [*sic*] active substances." (12/28/04 Office Action, page 8).

Concerning the Examiner's statements, Applicants respectfully point out that Ekman simply does not teach "further encapsulation" of a microparticle in the sense that "further encapsulation" equates with "coating the surface of" a pre-formed, solid microparticle. Rather, Ekman teaches encapsulating, (i.e., entrapping or enclosing), a macromolecular substance within a microparticle during the formation of the microparticle via Ekman's disclosed two-phase liquid method of microparticle formation.

Additionally, there is no suggestion in Woiszwillo, which teaches a fast and economical, non-emulsion-type system for preparing microparticles, that it would be suitable or desirable to use the two-phase emulsion-based system of Ekman to make microparticles. Contrary to the Examiner's statements, there is no desirability obtained from Ekman to "further encapsulate" the microparticles of Woiszwillo, because Ekman does not teach "further encapsulating" in the sense of applying a coating of a polymer onto the outer surface of the finished, solid microparticle product. Instead, Ekman teaches entrapping, enclosing or encapsulating (all synonymous terms) a macromolecular substance so as to be contained in the microparticle product as part of Ekman's disclosed method of making microparticles that contain various macromolecules. Ekman also does not remotely teach or disclose a method of making microparticles that involves coating pre-formed, solid particles with an outer shell of a release rate-controlling polymer, where an organic solvent would be used.

Applicants respectfully disagree that one skilled in the art would have been motivated to combine the teaching of Woiszwillo with the teaching of Ekman to "further encapsulate" the microparticles prepared by Woiszwillo's method so as to increase stability of the biologically active substances, as opined by the Examiner on page 10 of the 12/28/04 Office Action. As discussed above, Ekman's use of the term encapsulation equates with entrapping or enclosing a macromolecule within microparticles during the formation of the microparticles by Ekman's

method. (See above and Col. 8, lines 8-28). There is no "further encapsulation" of microparticles in Ekman's method. Thus, Ekman's teaching is not remotely the same as Applicants' claimed invention in which a release-rate controlling polymer coating is applied as an outer shell to already-formed, solid starch microparticles. Moreover, both Woiszwilllo and Ekman in combination are silent regarding a release rate-controlling polymer shell that is applied as an external coating on the outer surface of the solid microparticles, particularly a polymer that is applied in the presence of organic solvent.

It is submitted that if one were to combine Woiszwilllo with Ekman, one would not be led to make the modifications necessary to achieve Applicants' presently claimed invention, based on the teachings of these references considered for all that they offer. Applicants respectfully disagree that one of ordinary skill in the art would have been motivated "to further encapsulate the Woiszwilllo microparticles by starch using Eckman's method" (12/28/04 Office Action, page 10), because Ekman does not remotely teach or suggest "further encapsulation of microparticles by starch." Therefore, the combination is inapplicable to the distinctly different method of Woiszwilllo and would not result in "further encapsulated" microparticles. Moreover, Ekman does not teach or suggest modifying microparticles by coating with starch. Without a suggestion or motivation in the references to combine their teachings, the § 103 rejection is inappropriate and should be withdrawn.

Finally, it is respectfully submitted that the tertiary reference of Laakso, which teaches that polyacryl starch may be used as a carrier for passive target drug delivery, and the quaternary reference of Takada, which teaches a sustained release formulation biologically active microparticles coated by copolymers of polylactic/glycolic acid, do not compensate for the severe deficiencies of the primary and secondary references in combination and thus do not render the presently claimed invention obvious, alone or in combination.

In view of the foregoing discussion and explanation, it is respectfully requested that the rejection under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

Applicants respectfully submit that the application is now in condition for allowance.
An action progressing this application to issue is courteously urged.

Should any additional fees be deemed to be properly assessable in this application for the timely consideration of this Amendment, or during the pendency of this application, the Commissioner is hereby authorized to charge any such additional fee(s), or to credit any overpayment, to Deposit Account No. **50-0311** (Reference No. 28069-594).

Should a further Extension of Time be required in connection with the filing of this Amendment, the Commissioner is hereby requested to grant any such Extension of Time as may be deemed necessary, and is authorized to charge any such Extension of Time Fee as may be required to keep the application in good standing, to Deposit Account No. **50-0311** (Reference No. 28069-594).

If the Examiner believes that further discussion of the application would be helpful, he is respectfully requested to telephone the applicants' undersigned representative at (212) 692-6742 and is assured of full cooperation in an effort to advance the prosecution of the instant application and claims to allowance.

Respectfully submitted,

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.

Date: April 27, 2005

By: Leslie A. Serunian
Leslie A. Serunian
Registration No. 35,353

Correspondence Address:

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
Chrysler Center
666 Third Avenue, 24th Floor
New York, New York 10017
Telephone: (212) 935-3000
Facsimile: (212) 983-3115
Direct Tel.: (212) 692-6742